REMARKS

Applicant's attorney wishes to thank the Examiner for the careful consideration given to the present application and the courteous interview extended to the undersigned, Ray Miller, and the co-inventor, Dr. Stuart Shanler, on October 7, 2008. Currently, claims 1 and 3-6 and 13-16 are pending. Claims 2, 7-12 and 17-24 are canceled. Claim 1 has been amended to clarify that the therapeutically effective amount of the at least one alpha-1 adrenoreceptor agonist treats rosacea, and further is applied topically to the skin of the subject. Support for such an amendment may be found at, for example, paragraphs [0044] and [0049] of the specification and claim 2 as originally filed. In addition, claim 1 has been amended to remove the term "cosmetically," as such a term is redundant. In addition, claims 14, 15 and 16 have been amended for purposes of clarity or proper format. Each of the objections and rejections set forth in the Office Action are addressed below in the order presented therein.

35 U.S.C. § 102(b)

The Examiner has rejected claims 1-3, 14 and 16 under 35 U.S.C. § 102(b) as allegedly being anticipated by Leal, email communication, (hereinafter referred to as "Leal") as evidenced by U.S. Publication No. 20030108496 to Yu (hereinafter referred to as "Yu"). Applicant respectfully disagrees. As will be discussed in greater detail below, neither Leal nor Yu satisfy the statutory requirements of prior art.

Leal is not prior art.[1] First and foremost, as noted in the Response to Non-final Office Action dated January 11, 2008, submission of Leal is not and can not be construed as an admission that the information is prior art or material to patentability. See MPEP § 2129 (IV). Applicant submitted Leal in compliance with its duty of candor and good faith with the Office, which requires Applicant to submit any information that *may* be material to patentability. MPEP § 2001.

[1] The position that Leal is not prior art applies to both the rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103.

It is respectfully submitted that Leal is not proper prior art under 35 U.S.C. § 102(b). In particular, Leal is not a "printed publication" within the meaning of 35 U.S.C. § 102(b). The touchstone of "printed publication" is public accessibility of the disclosure. Leal fails miserably to satisfy this requirement. Thus, the question to be examined under 35 U.S.C. § 102(b) is the accessibility to at least the pertinent part of the public, of a perceptible description of the invention, in whatever form it may have been recorded. Access involves such factual inquiries as classification and indexing. A reference is considered a "printed publication" and a bar to patentability "upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation." *In re Wyer*, 655 F.2d 221 (CCPA 1981). Factors often considered by the courts include (i) whether there was a subject matter index, some type of systematic index or catalogue of the materials or any searching methods available for the "database" or materials; and/or (ii) whether the materials was intended to be made available to the public.

While courts have held that the lack of a subject matter index is not necessarily dispositive, ultimately, a critical question is whether a person skilled in the art would have been able to find the document. *See In re Wyer,* 655 F.2d at 226-27 (finding a microfilmed Australian patent application on file and open to public inspection at the Australian Patent Office and five sub-offices sufficiently accessible); *In re Cronyn,* 890 F.2d 1158 (Fed. Cir. 1989) (finding three undergraduate theses, referenced only by index cards filed alphabetically by author and held in a shoebox in the chemistry department, inaccessible to the public). *Cronyn* involved college students' presentations of their undergraduate theses to a defense committee made up of four faculty members. Their theses were later catalogued in an index in the college's main library. The index was made up of thousands of individual cards that contained only a student's name and the title of his or her thesis. The index was searchable by student name and the actual theses themselves were neither included in the index nor made publicly accessible. The Federal Circuit held that because the theses were only presented to a handful of faculty members and "had not

been cataloged [sic] or indexed in a meaningful way," they were not sufficiently publicly accessible for the purposes of 35 U.S.C. § 102(b). *In re Cronyn,* 890 F.2d at 1161.

Another factor considered by courts is whether the reference was intended to be made available to the public. *See, e.g., In re Wyer,* 655 F.2d at 222 (stating that 'intent to make public' is one factor, among many, in "determining whether an item may be termed a 'printed publication'"); *Bristol-Myers Squibb Co. v. Boehringer Ingelheim Corp.,* 86 F. Supp. 2d 433, 444 (D.N.J. 2000), *aff'd in part, vacated in part on other grounds,* 246 F.3d 1368 (Fed. Cir. 2001) (stating "the intent behind distribution is key').

In the instant case, Leal is not a "publication" under 35 U.S.C. § 102(b) because it there is not a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation. Based upon our understanding, Leal was posted on a "listserv" called RxDerm-L. RxDerm-L is an electronic mailing list that is only provided to and/or accessible to a limited number of individuals who actually subscribe to the list. The information posted on RxDerm-L is not viewable by anyone in the public who is not a member of the electronic mailing list. There does not appear to be any subject matter index or catalogue of the materials that have been posted on RxDerm-L by subscribers to RxDerm-L, let alone the public, and further there is no method to search RxDerm-L by subscribers to RxDerm-L, let alone the public. There does not appear to be any archive of the information posted on the Rx-Derm-L listserv. One ordinarily skilled in the art would not be able to access RxDerm-L, let alone be able to find Leal using reasonable diligence (or any diligence) once they could otherwise access RxDerm-L. Furthermore, the members of RxDerm-L do not expect that the material posted will be publicly available, as access to the email listings is limited only to subscribing members. Accordingly, for the foregoing reasons, it is respectfully submitted that Leal can not be considered a "printed publication" within the meaning of 35 U.S.C. § 102(b), and therefore is not available as prior art under 35 U.S.C. § 102(b).

When the Federal Circuit recently addressed an analogous situation in *SRI Int'l v. Internet Security Systems*, the Federal Circuit vacated the district court's decision - finding a lack of evidence that SRI's prior publication was sufficiently publicly available more than one year before the patent applications were filed. *SRI Int'l v. Internet Security Sys.* 511 F.3d 1186 (Fed. Cir. 2008). In *SRI*, the reference was e-mailed to a conference chair and posted the paper on an accessible SRI FTP site as a "backup" for the conference chair, and the reference remained on the FTP site for seven days, all of which occurred more than one year prior to the filing date of the application. The Federal Circuit found insufficient evidence to rule on summary judgment, noting that while the FTP server was publicly accessible, it was uncataloged and would have been difficult to search. Additionally, only one non-SRI person (the conference chair) was shown to have knowledge of the paper on the FTP site. Thus, the court vacated summary judgment for further development of the facts.

It is respectfully submitted that Leal is not proper prior art because it was not accessible to the public; it has not been catalogued, indexed, or archived , it is not searchable by the public, and it was not intended for public consumption. Notwithstanding the foregoing, as will be discussed in greater detail below, even if Leal is deemed prior art by the Examiner, it does not anticipate or render obvious the present claims.

Yu is not prior art.[2] Initially, it is respectfully submitted that Yu (the non-provisional application) is not proper prior art under 35 U.S.C. § 102(e) to the present application as relied upon by the Examiner. In particular, the present application was filed on January 22, 2004 and the Yu non-provisional application was filed on April 2, 2004 (after the filing date of the present application). Although Yu claims priority to Provisional Application No. 60/460,322 filed on April 4, 2003 (hereinafter referred to as the '322 Provisional Application"), the '322 Provisional Application is different and fails, in Applicant's opinion, to disclose the subject matter relied upon by the Examiner in this rejection. In particular, the '322 Provisional application fails to disclose a method for treating rosacea by topically administering to the skin a

[2] The position that Leal is not prior art applies to both the rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103.

therapeutically effective amount of at least one α_1 adrenoreceptor agonist as recited in the pending claims. This is not a technicality as the Yu non-provisional application and the Yu '322 Provisional Application are different. The '322 Provisional Application discloses the use of antioxidant polyhydroxy-lactones for the treatment of reactive blood vessels, and lumps rosacea into these conditions However, the '322 Provisional Application only provides evidence that that topical administration of a polyhydroxy-lactone was effective in reducing the erythema associated with nummular eczema (see Example 1). First, erythema may be caused by a number of disorders, and the effective treatment of erythema of one disorder (nummular eczema) does not allow one skilled in the art to extrapolate such a finding to erythema caused by a different disorder (rosacea). More importantly, with respect to oxymetazoline itself, the '322 Provisional Application is silent as to an effective amount of oxymetazoline to treat rosacea or whether it is even effective to treat rosacea or erythema at all. It is merely listed as an additional agent that could be incorporated into the polyhydroxy-lactone composition among myriad other agents (see paragraph [0014] and [0015] of '322 Provisional Application). Many of these additional agents are know to exacerbate erythema in general, and rosacea in particular. The Examiner's reliance on Yu is misplaced, but if the Examiner insists on relying on a reference that teachings nothing relevant about oxymetazoline or rosacea, then she must use rigor and at least rely on the '322 Provisional Application to the extent possible as the basis of the rejection.

Leal as evidenced by Yu fails to anticipate the pending claims. In the event that the Office disagrees with the Applicant as to the characterization of Leal, it is respectfully submitted that Leal in view of Yu fails to anticipate the present claims. That is, Leal in view of Yu does not disclose a method for treating rosacea comprising topically administering to the skin a therapeutically effective amount of at least one alpha-1 adrenoreceptor agonist (e.g., oxymetazoline), wherein said alpha-1 adrenoreceptor agonist treats rosacea as set forth in pending claim 1.

Leal purports to report that "redness" or "facial erythema" for two patients with acne was decreased upon application of oxymetazoline, and provides "before" and "after" pictures of the two subjects purportedly supporting this observation. There is no statement that these subjects have rosacea, and in fact, as supported by Leal, appear to be afflicted with acne,

and in particular with erythema associated with acne. As understood by one ordinarily skilled in the art, erythema associated with **acne** and erythema associated with **rosacea** are two completely different conditions with different pathophysiologies. As evidenced by Harper, "An update on the pathogenesis and management of acnes vulgaris" 51(1) J. AM. ACAD. DERMATOL. S36 (2004) attached hereto as ***Exhibit A***, erythema associated with acne is due to an inflammatory process (see page S36, Col. 1, second paragraph). Erythema associated with acne does not involve any abnormal blood vessel reactivity. In contrast to the well described pathophysiology of acne, the exact pathophysiology of rosacea has yet to be fully elucidated, however significant scientific evidence supports a primary mechanism of abnormal blood vessel reactivity. The pathophysiology of rosacea and the pathophysiology of acne are known, however, to be quite distinct. One ordinarily skilled in the art would not understand Leal as evidencing the effective use of oxymetazoline for the treatment of rosacea, but only as suggesting the potential use of oxymetazoline for the treatment of erythema associated with acne. Furthermore, one ordinarily skilled in the art would not extrapolate the use of oxymetazoline for the treatment of erythema of acne to the treatment of rosacea because the two conditions are unrelated and involve different pathophysiologies.

Yu fails to evidence that the treatment of erythema is an effective treatment of rosacea or otherwise cure such a deficiency. Yu lumps together a large number of conditions as being associated with "reactive blood vessels" including, for example, rosacea, eczema, psoriasis etc. However, it is important to note that symptoms of a disorder (erythema) should not be confused with a disorder that causes the symptoms (i.e., rosacea). Erythema is a symptom of many disorders including rosacea. However, treatment of erythema of one disorder does not disclose or even suggest that the erythema of different disorder could be treated absent a specific teaching because the etiologies of such disorders are vastly different or not even understood by those skilled in the art. Yu only provides evidence that topical administration of a polyhydroxy-lactone (i.e., gluconolactone) was effective in reducing the erythema associated with nummular eczema and further states and extrapolates that this compound would be effective in treating rosacea (see Example 1), however Yu is silent as to the effectiveness of oxymetazoline or any other alpha-1 adrenoreceptor agonist for rosacea.

One ordinarily skilled in the art would not have found it obvious or have been motivated to treat rosacea by topically administering to the skin an effective amount of an α_1 adrenoreceptor agonist as recited in the pending claims because the '322 Provisional Application fails to teach or suggest that an α_1 adrenoreceptor agonist is effective for treating erythema associated with rosacea or even that an α_1 adrenoreceptor agonist is effective for treating erythema.

Additionally, it is respectfully submitted that in order for a reference to be considered prior art it must be enabling. That is, the disclosure of the reference must be sufficient to put one skilled in the art in possession of the invention or otherwise teach one skilled in the art to make or carry out the clamed invention without undue experimentation. *Impax Laboratories, Inc. v. Aventis Pharmaceuticals Inc.*, 496 F. Supp. 2d 428, 432 (D. Del. 2007), *aff'd* ___ F.3d ___ (Fed. Cir. 2008) (citing *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *Minnesota Mining and Manufacturing Co., v. Chemque, Inc.*, 303 F3d. 1294, 1301 (Fed. Cir. 2002)).

Enablement in this context hinges on undue experimentation, which is evaluated from the vantage point of those experienced in the field of the invention. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed...." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). Factors relevant in determining whether undue experimentation is required include: (1) the quantity of experimentation; (2) the amount of direction or guidance present; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

In *Impax Labs*, the Federal Circuit affirmed the district court's finding that the cited art was not enabled, and therefore failed to anticipate the claims of the subject patent. In particular, the prior art reference disclosed Formula I, a genus of compounds that included the specific compound riluzole, and further disclosed that the compounds would be useful in the

treatment of certain diseases, including neurological diseases in which glutamate may be implicated, such as amyotrophic lateral sclerosis (ALS) and dosage guidelines for the genus of compounds. The prior art reference also disclosed the specific compound riluzole. The claims at issue, which were allegedly anticipated by the prior art reference, were directed to a method of treating a mammal with ALS by administering an effective amount of riluzole. In holding that the prior art reference was not enabled, the district court remarked that nothing in the prior art reference directs one skilled in the art to recognize that riluzole can be used to treat ALS, and the mere mention of riluzole is not sufficient to put one skilled in the art of possession of the claimed invention as required to support a conclusion of enablement. *Impax Laboratories,* 496 F. Supp. 2d at 432. The court further remarked that the dosage guidelines disclosed in the reference were broad and not specific to any of the compounds of Formula I and that reference associated the compounds with the treatment of at least eight different diseases, and there was nothing in the prior art reference that would lead one ordinarily skilled in the art to recognize that any specific compound, let alone riluzole, would be used to treat any specific disease, let alone ALS. *Id.* at 433. The district court stated that the link between riluzole and the treatment of ALS was speculative, and undue experimentation would be required to establish such a link. *Id.* Accordingly, the prior art reference was held to be non-enabled, and therefore failed to anticipate the subject claims.

As was again confirmed in the recently decided *Impax Laboratories*, discussed above, there is no disclosure in the '322 Provisional that would lead one ordinarily skilled in the art to recognize that oxymetazoline or any other α_1 adrenoreceptor agonists would be effective in treating any erythema, and in particular rosacea or even erythema associated with rosacea. The '322 Provisional fails to disclose any link between oxymetazoline and rosacea and undue experimentation would be required to establish such a link. Only with Applicant's work, as disclosed in the present application, would one ordinarily skilled in the art recognize that α_1 adrenoreceptor agonists, including oxymetazoline, actually treat rosacea and the erythema associated with rosacea by topically administering an effective amount to the skin.

Accordingly, Leal in view of Yu fails to anticipate and/or render obvious the present claims, and this rejection should be withdrawn.

35 U.S.C. § 103

The Examiner has rejected claims 13 and 15 under 35 U.S.C. § 103(a) as purportedly being unpatentable over Leal in view of Yu. For the reasons set forth above, Leal in view of Yu fails to anticipate and/or render obvious the present claims, and this rejection should be withdrawn.

The Examiner has rejected claims 1-3 and 13-16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yu in view of Applicant's statements in the specification (referenced as specification, page 1, background of the invention, paragraphs 1 and 2; page 7, lines 16-17). Applicant respectfully disagrees.

As set forth above, the Yu '322 Provisional in combination with Applicant's statements fail to disclose or suggest to one ordinarily skilled in the art that oxymetazoline or any other α_1 adrenoreceptor agonists would be effective in treating any erythema, and in particular rosacea or even erythema associated with rosacea. The '322 Provisional fails to disclose any link between oxymetazoline and rosacea Only with Applicant's work, as disclosed in the present application, would one ordinarily skilled in the art recognize that α_1 adrenoreceptor agonists, including oxymetazoline, actually treat rosacea and the erythema associated with rosacea by topically administering an effective amount to the skin.

In light of the remarks and amendments presented herein, it is believed that pending claims 1, 3-6 and 13-16 are in condition for final allowance and notice to such effect is respectfully requested.

CONCLUSION

Applicant has timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicant's attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,

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An update on the pathogenesis and management of acne vulgaris

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Acne vulgaris is an easily recognizable dermatologic disease. It is also very common. Acne is seen in nearly 100% of individuals at some time during their lives. Small, noninflamed acne lesions may not be more than a slight nuisance but, in individuals with more severe inflammatory nodular acne, pain, social embarrassment, and both physical and psychological scarring can be life altering. Fortunately, our understanding of the pathogenesis of acne has progressed and our therapeutic armamentarium has greatly expanded in the last twenty-five years.

The four key pathogenetic factors of acne have been recognized for decades. These include follicular epithelial hyperproliferation and resultant follicular plugging, excess sebum, inflammation, and the presence and activity of *Propionibacterium acnes* (Table I). The earliest microscopic lesion observed in acne vulgaris is the microcomedo. This lesion is characterized by follicular plugging. Inflammation and the bacteria, *P acnes*, are not observed. The stimulus for microcomedo formation is still unknown. Leading hypotheses implicate androgen hormones, alterations in follicular linoleic acid levels, and the inflammatory cytokine interleukin-1α (IL-1α). The microcomedo is the precursor of other acne lesions. With time, the microcomedo fills with *P acnes*, whose cell wall and biological byproducts are chemoattractant and proinflammatory. As a result, inflammatory cells surround the follicle, diffuse through the follicular wall, and produce enzymes that disrupt the follicular wall. The degree of inflammation seen in acne vulgaris may be dependent upon individual immune responsiveness to *P acnes*. Likewise, there may be individual variability in the response of the sebaceous gland androgen receptor to circulating androgens.

Recently, the toll-like receptor 2 (TLR-2) has been implicated in the pathogenesis of acne. TLR-2 is a pattern recognition receptor that is activated by *P acnes*. When bound, TLR-2 activates a transcription factor that upregulates production and the release of proinflammatory cytokines like interleukin-12 and interleukin-8 from monocytes. TLR-2 is expressed on infiltrating inflammatory cells around the pilosebaceous follicle in those with acne. Its expression increases as the acne lesion ages and becomes more inflamed.[1]

The role of androgen hormones in the pathogenesis of acne has also been carefully evaluated. Overall, circulating androgen hormone levels are normal in individuals with acne who do not have other signs or symptoms of hyperandrogenism. The enzyme 5α-reductase type 1 has been studied in those with and without acne. 5α-reductase type 1 is present in the sebaceous gland and converts testosterone to the more potent androgen receptor ligand, dihydrotestosterone (DHT). It has been hypothesized that those with acne might have more active 5α-reductase type 1. However, no statistically significant difference in enzyme activity has been observed to date between those with and without acne, but subject numbers have been very low.[2]

The past twenty-five years have brought about significant changes in the treatment of acne. No other group of medications has altered the management of acne more than the retinoids. The topical retinoids became mainstream acne treatment in the early 1980s, but problems with skin irritation limited their utility in some individuals. Adapalene, a topical retinoid by function, was introduced in the mid-1990s, followed quickly by formulations of tretinoin touted to be less irritating. Tazarotene was soon added to the list of topical retinoids effective in the treatment of acne. Topical retinoids have been well accepted as the treatment of choice for comedonal acne since their inception. Recently, they have been promoted as an effective treatment for inflammatory acne, alone or in combination with other acne

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EXHIBIT
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Table I. Acne treatments and their mechanism of action in acne vulgaris

Benzoyl peroxide	Antimicrobial Weakly comedolytic
Topical retinoids	Comedolytic Anti-inflammatory
Systemic antibiotics	Anti-inflammatory Antimicrobial
Oral contraceptives	Sebosuppressive
Systemic retinoids	Comedolytic Anti-inflammatory Sebosuppressive Indirectly antimicrobial

Acne vulgaris is a multifactorial disease process. Multiple treatments are available that target one or a few of the key pathogenetic elements. The most effective available drug, the systemic retinoid isotretinoin, targets all four of the primary follicular changes observed in acne vulgaris.

medications, and have been recommended for maintenance therapy after acne has been effectively controlled.

Isotretinoin, a systemic retinoid, was approved for use in acne vulgaris in 1982. It is arguably the most effective acne medication available, offering a durable clearing of acne lesions in 85% of its users. A long list of potential side effects limits its use to those individuals with severe, scarring acne or to individuals who do not respond to first-line topical and systemic acne treatments. Of the potential side effects, teratogenic effects and potential psychiatric disturbances have received the most attention in the lay press. The alleged risk of depression and other psychiatric disturbances and a need to decrease the number of isotretinoin-exposed pregnancies has prompted the development of a national registry of prescribing physicians.

Antibiotics continue to play an integral role in the management of acne. Tetracycline has fallen from favor in the face of increasing *P acnes* antibiotic resistance. Doxycycline and minocycline have replaced tetracycline as first-line anti-acne antibiotics. Low-dose doxycycline (doses below the minimal inhibitory concentration for *P acnes*) have recently been shown to be effective in the treatment of acne. These doses of doxycycline do not alter the microbial colony counts in acne patients and yet acne improves. Low-dose antibiotics maintain their anti-inflammatory properties and, though they do not decrease microbial colony counts, likely render *P acnes* less biologically active and less capable of inciting further inflammation.[3]

Long-term use of antibiotics in the acne population has raised concerns regarding the development of colonization with potential pathogens and bacterial resistance. *P acnes* resistance to tetracycline is well known to dermatologists. However, it is the antibiotic resistance of potential pathogens like *Streptococcus pyogenes* and *Staphylococcus aureus* that cause concern. A recent report found a threefold increase in the prevalence of *Streptococcus pyogenes* in the oropharynx of those acne patients treated with systemic or topical antibiotics compared with acne patients not receiving antibiotics. Eighty-five percent of *S pyogenes* cultured from those individuals on antibiotics was resistant to at least one tetracycline antibiotic. Although no significant difference in the frequency of illness was observed when the two groups were surveyed, it cannot be assumed that the changes in microflora and bacterial resistance in those on antibiotics for acne is not clinically significant.[4]

Topical benzoyl peroxides have been used to treat acne for years. Benzoyl peroxides are known to be antimicrobial and also have weak comedolytic properties. Despite the development of better comedolytic agents and the presence of numerous antibiotics and antimicrobials marketed for acne, benzoyl peroxides may be an even more important acne treatment option now than before. While *P acnes* has developed a considerable amount of resistance to erythromycin and tetracycline, benzoyl peroxide continues to effectively eradicate this acne-associated bacteria. Bacterial resistance to benzoyl peroxide has not been reported. In fact, combining benzoyl peroxide with topical or systemic antibiotics may decrease the development of resistance to the co-administered antibiotic.

Oral contraceptives have become an accepted therapeutic alternative for the treatment of acne in women. All combination oral contraceptive pills have a net effect of increasing sex hormone binding globulin and decreasing circulating free testosterone and therefore, have the potential to improve acne. A unique combination oral contraceptive, Yasmin, combines ethinyl estradiol with the progestin drospirenone. Drospirenone is an analog of spironolactone and has antiandrogenic and antimineralocorticoid properties. The drospirenone component in Yasmin is equivalent to 25 mg of spironolactone. Yasmin has been compared to a cyproterone acetate-containing oral contraceptive in the treatment of acne vulgaris and was found to be at least equally effective.[5]

Procedure-oriented acne treatments are being introduced nearly everyday. Light, laser, and photodynamic treatments are all currently being utilized in the treatment of acne. Blue and red light target different pathogenetic factors in acne. Blue light (405-420nm) reacts with porphyrins produced by

P acnes, creating reactive oxygen species that damage the bacterial cell wall and cause bacterial death. Red light (660nm) is anti-inflammatory. Both wavelengths of light may improve acne in some individuals. Clinical trials are few in number and offer no long-term follow-up to date. Photodynamic therapy (PDT) again utilizes blue light reacting with a porphyrin in the sebaceous gland. Sebaceous gland damage and destruction is the hypothesized mechanism of action of PDT in acne vulgaris. Controlled clinical trials are lacking at this time. Nonablative radiofrequency for the treatment of moderate to severe acne was recently reported in the dermatology literature. Nonablative radiofrequency produces dermal heat without causing epidermal damage. It is hypothesized to target the sebaceous gland in acne and to remodel acne scarring. Twenty-two subjects with moderate to severe, scarring, cystic, active acne were enrolled in the study. Study subjects received one initial treatment that lasted 30 to 45 minutes. Pain was managed with topical ELA-max. Patients were offered a second treatment after one month if no improvement was observed. Thirteen patients had only one treatment while only two patients required three treatment sessions. Seventy-five percent reduction in active acne lesion counts was measured in 18 of 22 subjects. Some improvement in acne scarring was also observed. Long-term results were not reported.[6] Lasers are also being used to cause sebaceous gland damage and destruction in individuals with acne vulgaris. Controlled clinical studies are still needed.

Remarkable progress has been made in our understanding of the pathogenesis of acne over the last twenty-five years, and improved treatment alternatives have changed the practice of dermatology and the lives of many of our patients. Much remains unknown. The search for the initial stimulus of microcomedo formation will continue. What is the role of IL-1α? What is the role of androgen hormones? What factors regulate the sebaceous gland?

Effective treatments that offer durable responses and have minimal side effects are still needed. The exact mechanism of action of isotretinoin is still unknown. It is unclear why treatment results are maintained in many individuals after discontinuation of the drug. A greater understanding of the mechanism of action of isotretinoin in acne will help us to design new drugs and procedures that are as effective as isotretinoin but avoid the unwanted side effects and associated risks.

Procedure-oriented acne treatments are not required to meet the stringent criteria set forth for prescription medications to become approved by the Food and Drug Administration. In order for these procedures to meaningfully contribute to the body of knowledge of acne and to help those individuals who suffer from acne, scientifically controlled clinical trials must be performed.

Much has been learned in the recent past about acne but even more is still unknown. Perhaps the next twenty-five years holds the key that will unlock many of the remaining mysteries. Perhaps we will find that key tomorrow.

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